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# The association of urinary sodium with incident apparent treatment resistant hypertension among African Americans: findings from the Jackson Heart Study

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Hypertension is a leading cause of cardiovascular disease and disproportionately affects African American (AA) adults. Apparent treatment-resistant hypertension (aTRH) is highly prevalent in this population. Sodium intake is associated with blood pressure (BP) levels, yet the relationship between sodium and the risk of developing aTRH in AA adults remains unclear. This study examined the association between 24-hour urinary sodium excretion and incident aTRH among AA adults with hypertension, using data from the Jackson Heart Study (JHS). The JHS included 5306 self-identified AA adults from Jackson, Mississippi, with data collected from 2000 to 2013. This analysis included 452 participants with baseline hypertension and complete urinary excretion and medication data. Sodium excretion was categorized into quartiles: Q1 (253 to 2530 mg/day), Q2 (2553 to 3657 mg/day), Q3 (3680 to 4692 mg/day), and Q4 (4715 to 9775 mg/day). A semi-parametric proportional hazards model was used to determine the association between sodium excretion and incident aTRH. Participants had a mean age of 63 years, and 27.7% were men. Over a median follow-up of 7.5 years, 123 participants (27.2%) developed aTRH. The incidence of aTRH was 25.7%, 24.8%, 29.2%, and 29.2% in Q1, Q2, Q3, and Q4 of urinary sodium excretion, respectively. In adjusted models, there was no significant association between urinary sodium excretion and incident aTRH [HRs (95% CIs): Q2 = 0.71 (0.34, 1.46), Q3 = 1.02 (0.50, 2.06), Q4 = 0.95 (0.46, 2.00); $P = 0.166$]. Among AA adults with treated hypertension, sodium intake, as measured by 24-hour urinary sodium excretion, was not significantly associated with incident resistant hypertension.

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## INTRODUCTION

Almost 1 in 3 American adults has high blood pressure (BP) [1], with less than half achieving adequate BP control, increasing their risk for heart disease and stroke. Hypertension contributes to 410,000 deaths annually and disproportionately affects minority populations, particularly African American (AA) adults, with significant financial and health impacts [2]. AA adults have higher rates of hypertension compared to White adults, contributing to a 5.5-year reduction in life expectancy for AA adults [3].

Reducing sodium intake is an effective strategy to lower BP and improve cardiovascular health [4–6]. The American Heart Association (AHA) recommends sodium intake of <2300 mg/day. However, most Americans consume an average of 3400 mg/day [7], with 86% of adults with hypertension exceeding the recommended limit [8]. AA adults consume more sodium than other racial or ethnic populations in the US due to greater consumption of processed foods, restaurant meals, salt added to home-cooked meals [9], along with systemic barriers like poverty [10]. Urinary sodium excretion is a reliable measure of dietary sodium intake [11], making it a robust measure for assessing sodium consumption [12].

Apparent treatment resistant hypertension (aTRH), defined as BP above target despite use of ≥3 classes of antihypertensive medication or ≥4 classes regardless of BP level, is a common clinical problem [13] and associated with increased cardiovascular risk [14]. AA adults are more likely to have resistant hypertension due to genetic predisposition to salt and water retention than White adults [15].

Current literature lacks robust evidence on the association between high-quality measures of sodium intake and risk of developing aTRH specifically in AA adults, who have hypertension. Studies demonstrating that reduced sodium intake significantly lowers BP in patients with resistant hypertension [4, 5] have limited external validity due to small sample sizes. Addressing

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these gaps is important for developing dietary and clinical interventions for this high-risk population. This study examined the association of sodium intake with incident aTRH among AA adults with hypertension from the Jackson Heart Study (JHS). We hypothesize a positive linear association between sodium intake, as measured by urinary sodium, and incident aTRH in this population.

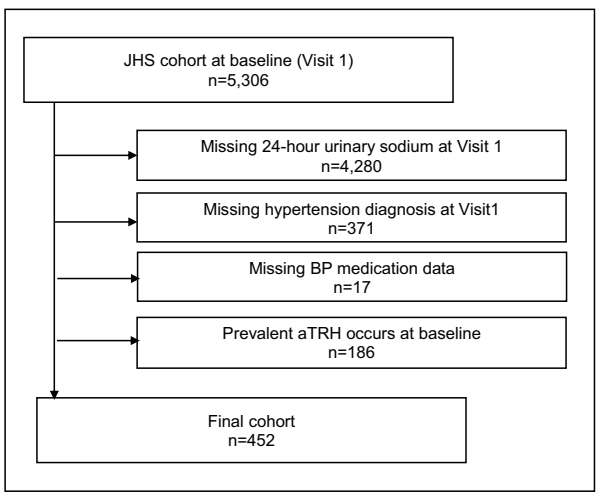
## METHODS

### Study population

The JHS is a prospective community-based observational study of risk factors for cardiovascular disease in AA adults. The JHS recruited 5306 adults aged 21–94 years, residing in the tri-county area of the Jackson, Mississippi, USA, metropolitan area. Participants were examined at baseline – Visit 1 (2000–2004) and two additional examinations: Visit 2 (2005–2008) and Visit 3 (2009–2013). Further details of the JHS study design, recruitment, and data collection were published previously [16–18]. The study was approved by the Institutional Review Boards of Jackson State University, Tougaloo College, and the University of Mississippi Medical Center in Jackson. All participants provided written informed consent. This article was reviewed by the JHS Publications and Presentations Committee and has been approved for publication. The study was reported following the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines [19].

### Inclusion and exclusion criteria

The JHS cohort included 5306 participants at Visit 1. We excluded 4854 participants, including those missing 24-hour urinary sodium data at Visit 1 ($n = 4280$), BP medication data ($n = 17$), or hypertension diagnosis ($n = 371$) and those with prevalent aTRH at baseline ($n = 186$) (Fig. 1). After applying these exclusion criteria, our analyses included 452 JHS participants with hypertension (defined as SBP ≥ 130 mm Hg or DBP ≥ 80 mm Hg, according to the 2017 ACC/AHA BP guidelines hypertension [14]) in the present analyses. Although limiting the sample to those who voluntarily provided 24-hour urinary sodium samples reduced the eligible number of participants, this approach was chosen because 24-hour urine measurements are considered the gold-standard biomarker of dietary sodium intake. While spot urine samples are more plentiful (approximately 863 participants), they provide less accurate estimates of daily oral sodium consumption [20–23]. With 24-hour urine measurements, we improve the precision and internal validity of our exposure assessment, thereby providing a more robust examination of the association between sodium intake and the development of aTRH. The trade-off of prioritizing measurement quality over sample size is critical given our primary objective of accurately characterizing the relationship between sodium intake and risk of incident aTRH.




This figure illustrates the selection process for the final sample of 452 participants from the initial 5,306 in the Jackson Heart Study.

**Fig. 1** Flowchart of Participant Selection.

### Data collection

JHS data were collected in two phases: an in-home interview followed by a clinical examination at the JHS clinic. During the in-home interview, participants provided information on their demographics (i.e., age, sex, education, income, and insurance status), lifestyle factors (smoking status, alcohol consumption, and physical activity), medical history (i.e., coronary heart disease history, stroke history, myocardial infarction history, chronic kidney disease history, and diabetes history) and medication use (i.e., statin use, and antihypertensive medication use– angiotensin-converting enzyme inhibitors–ACEI, angiotensin II receptor blockers–ARB, beta-blockers, calcium channel blockers–CCB, diuretics, and other hypertensive medication classes) [18]. The JHS physical activity instrument was also administered to assess participants' physical activity levels as poor, intermediate, or ideal/recommended [24, 25].

During the clinic visit, medication adherence was assessed by reviewing the participants' pill bottles to record the medications taken in the two weeks before the visit. A standardized protocol was used to conduct physical assessments and collect biological samples. BP, height, and weight were measured, and blood and urine samples were obtained. BP was based on the average of two seated measurements, taken with an appropriate cuff size and a standard Hawksley random zero sphygmomanometer (Hawksley and Sons Limited). Participants rested for five minutes before the first measurement, with a 30-second interval between measurements. The raw BP data obtained from the random zero sphygmomanometers were subsequently calibrated using robust regression models [26]. Diabetes was defined as either a fasting plasma glucose ≥126 mg/dL, hemoglobin A1c ≥ 6.5%, current use of diabetes medication, or a physician report of the condition [27]. Total cholesterol, low-density lipoprotein (LDL), and high-density lipoprotein (HDL) levels were measured from fasting blood samples using standardized enzymatic methods. Body mass index (BMI) was calculated as weight (kg)/height (m)2. Fasting serum glucose was measured using the glucose oxidase method on a Vitros 950 or 250 analyzer (Ortho Clinical Diagnostics). Glycated hemoglobin was assessed using a Tosoh high-performance liquid chromatography system (Tosoh Corporation). C-reactive protein (CRP) was assessed using the immunoturbidimetric CRP-Latex assay on a Hitachi 911 analyzer, utilizing high-sensitivity C-reactive protein (hs-CRP) measurements that can detect smaller increases in CRP compared to standard tests [28].

Further, urine samples were analyzed to measure sodium intake and albumin levels using the Dade Behring BN II nephelometer (Siemens), based on the specimens collected during the baseline study visit [29]. All willing participants were invited to provide a single 24-hour urine samples and they were provided with instructions and a urine collection kit to complete this process [30]. A single 24-hour urine collection was selected to minimize any potential negative impact on cohort retention [30]. JHS staff verbally ensured that participants understood the collection procedures, and participants collected all urine over a 24-hour period, with collection jars labeled with participant ID, and collection times. However, only 1026 participants completed the 24-hour urine collection. Serum and urine creatinine concentrations were measured using a multi-point enzymatic spectrophotometric assay on a Vitros 950 Ortho Clinical Diagnostics analyzer. For analysis purposes, the creatinine values were biochemically calibrated to the Cleveland Clinic–equivalent Minnesota Beckman CX3 assay [29, 31]. Urinary albumin-to-creatinine ratio (ACR) was generated by dividing the albumin levels by the creatinine values. Estimated glomerular filtration rate (eGFR) was calculated via the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation [32].

### Exposure

The main exposure was 24-hour urine sodium excretion, expressed as milligrams (mg) at Visit 1. Participants were stratified into quartiles based on their urinary sodium levels: Q1 ($n = 113$, 253 - 2530 mg/day); Q2 ($n = 113$, 2553 - 3657 mg/day); Q3 ($n = 113$, 3680 - 4692 mg/day), and; Q4 ($n = 113$, 4715 - 9775 mg/day).

### Outcome

The outcome variable was incident aTRH at visits 2 or 3. Participants with uncontrolled BP (i.e., SBP ≥ 130 mm Hg or DBP ≥ 80 mm Hg, according to the 2017 ACC/AHA BP guidelines and the 2018 AHA Scientific Statement on resistant hypertension [14]) while taking three classes of antihypertensive medication or controlled BP (i.e., SBP < 130 mm Hg and DBP < 80 mm Hg) while taking four or more classes of antihypertensive medication, were classified with aTRH [13, 14, 29].

### Covariates

Covariates included demographic variables, lifestyle factors, antihypertensive medication use, medication adherence, BMI, fasting cholesterol (total, low-density lipoprotein–LDL and high-density lipoprotein–HDL), urinary albumin-to-creatinine ratio (ACR), and C-reactive protein (CRP).

### Statistical analysis

Baseline characteristics across quartiles of urinary sodium were examined. Normally distributed continuous data were presented as mean ± standard deviation, while non-normally distributed continuous data were expressed as median (Q1, Q3). Categorical variables were presented as percentages. We used histograms to display the baseline distribution of 24-h urinary sodium levels (Supplementary Figure 1). Missingness in baseline characteristics are presented in Supplementary Table 1, and analysis comparing baseline characteristics of participants with and without urinary sodium measurements are presented in Supplementary Table 2.

To account for missingness in the baseline covariates, we used multiple imputation via chained equations with guidelines relevant for interval-censored data [33, 34]. Briefly, we included in our imputation model all baseline covariates, the exposure, aTRH event indicator, and the cumulative baseline hazard. We had at least as many imputed datasets as the percentage of individuals with any missing data (approximately 24%). Rubin's rules were adopted for combining estimates and standard errors across the imputed datasets [35].

We examined the association between 24-h urinary sodium excretion and incident aTRH using a semi-parametric proportional hazards regression model for interval-censored data [36], adjusting for potential confounders. In Model 1, we adjusted for age and sex. For Model 2, additional adjustments were made for smoking status, alcohol consumption, physical activity, BMI, diabetes, history of coronary heart disease, history of stroke, heart failure, chronic kidney disease, estimated glomerular filtration rate, low- and high-density lipoproteins, urinary albumin-to-creatinine ratio, medication adherence, and an indicator for each antihypertensive medication class. In Model 3, we made additional adjustments for income, education and insurance status. As a secondary assessment, we conducted a sensitivity analysis using the subset of participants with spot urine sodium measurements to evaluate the robustness of our findings. This analysis remained consistent with the primary modeling approach, and corresponding results are presented in Supplementary Table 3.

Hazard ratios (HRs) for incident aTRH were estimated using quartiles of urinary sodium, with the lowest quartile (Q1) as the reference. We visualized cumulative incidence curves for incident aTRH by quartiles of urinary sodium using Turnbull's estimator [37]. Participants who did not develop aTRH were right censored at their last follow-up visit, while those who developed aTRH were left or interval-censored, as appropriate. Assuming a proportional hazards model, we graphed HRs for incident aTRH associated with urinary sodium using restricted quadratic splines with a single knot specified at the median value. Analyses were conducted using R version 4.3.2 [38]. We used the mice and icenReg packages available in R to run multiple imputation and fit all models appropriate for interval-censored data respectively [39, 40]. The code used to generate the results presented in this study is available upon reasonable request from the corresponding author.

## RESULTS

### Participant characteristics

The baseline characteristics of the 452 included participants are presented in Table 1 (median age 63.0 years; 27.7% men). Participants were stratified into four groups based on their 24-h urinary sodium excretion levels: Q1 (253 to 2530 mg/day), Q2 (2553 to 3657 mg/day), Q3 (3680 to 4692 mg/day), and Q4 (4715 to 9775 mg/day). The overall median 24-h urinary sodium excretion was 3669 (2547, 4698) mg/day and the distribution is presented in Supplementary Figure 1.

Compared to those with lower urinary sodium levels, a larger proportion of participants with higher urinary sodium levels were younger, female, have higher income, consume alcohol, and used any antihypertensive medication class. Additionally, participants in higher urinary sodium had higher BMI, higher eGFR levels, or lower HDL cholesterol levels. Conversely, higher urinary sodium levels were less common among participants with a history of stroke, chronic kidney disease and those using ACEIs and beta-blockers.

### Association between urinary sodium and incident aTRH

Table 2 presents the incidence rates and HRs for aTRH, by quartile. Over a median follow-up of ~7.5 years, 123 participants (27.2%) developed aTRH. Q3 and Q4 showed the highest incident aTRH, each with 33 cases (29.2%), while Q1 had the lowest incidence, with 29 cases (25.7%). The cumulative incidence curve for incident aTRH by quartiles of 24-h urinary sodium excretion (Fig. 2) shows that individuals with higher urinary sodium levels (Q3 and Q4) had higher risk of developing aTRH over time compared to those with lower sodium levels.

In the adjusted model (Model 3), the associations between 24-h urinary sodium excretion and incident aTRH did not reach statistical significance. Relative to Q1, the HRs with 95% confidence intervals (CIs) for Q2, Q3 and Q4 were 0.71 (0.34, 1.46), 1.02 (0.50, 2.06), and 0.95 (0.46, 2.00), respectively ($P = 0.166$). As shown in Fig. 3, the HR for incident aTRH across restricted quadratic splines of urinary sodium (mg/day) indicated a non-linear association. While both very low and very high 24-h urinary sodium excretion levels were associated with a lower risk of aTRH, the highest risk occurred within the Q3 range.

## DISCUSSION

This study examined the association between urinary sodium and incident aTRH among African American adults. Over a median follow-up of ~7.5 years, 123 participants (27.2%) developed aTRH and there was no statistically significant association between urinary sodium and incident aTRH. The median 24-h urinary sodium excretion among JHS participants with hypertension was 3669 mg/day, exceeding both the AHA recommendation of <2300 mg/day, the national average intake of 3400 mg/day [7], and other similar cohort studies [41–43]. This finding reinforces evidence of high sodium consumption among AA adults [44], with critical implications for the increasing incidence of hypertension-related complications, such as stroke and heart disease, in this population [45]. This finding also underscores the urgent need for targeted public health interventions to reduce sodium intake within the AA community to prevent worsening health disparities.

The adjusted model did not demonstrate evidence of association between 24-hour urinary sodium excretion and incident aTRH over a median follow-up of ~7.5 years. The HRs for Q2, Q3, and Q4 compared to Q1 showed wide confidence intervals, especially at the extremes of sodium intake, indicating substantial variability in the estimates. This suggests that while the associations were not statistically significant, the potential for both protective and adverse effects of urinary sodium excretion on incident aTRH remain possible. Our findings also suggest a nonlinear association between urinary sodium and aTRH in this cohort, indicating that the role of sodium excretion in developing hypertension-related outcomes may be more complex than previously thought [42]. It is also possible that other unmeasured factors, such as genetics, other dietary components like potassium [46] or clinical conditions, could influence this association, and further research is needed to explore whether subgroups of individuals may exhibit different patterns. Therefore, a comprehensive approach to hypertension management, one that considers multiple factors in addition to sodium intake, is needed to effectively address the risk of aTRH.

Baseline characteristics revealed some variations in participants' characteristics by sodium levels, highlighting the complex interplay between sodium intake and demographic, lifestyle and clinical factors. Participants with higher sodium levels were younger, more likely female, had higher income, consumed alcohol, adhered to antihypertensive medications, had higher BMI, higher eGFR, and lower HDL cholesterol. These findings suggest

**Table 1.** Baseline characteristics of JHS participants enrolled in 2000–2004 and included in the analysis of incident aTRH overall by quartiles of urinary sodium.

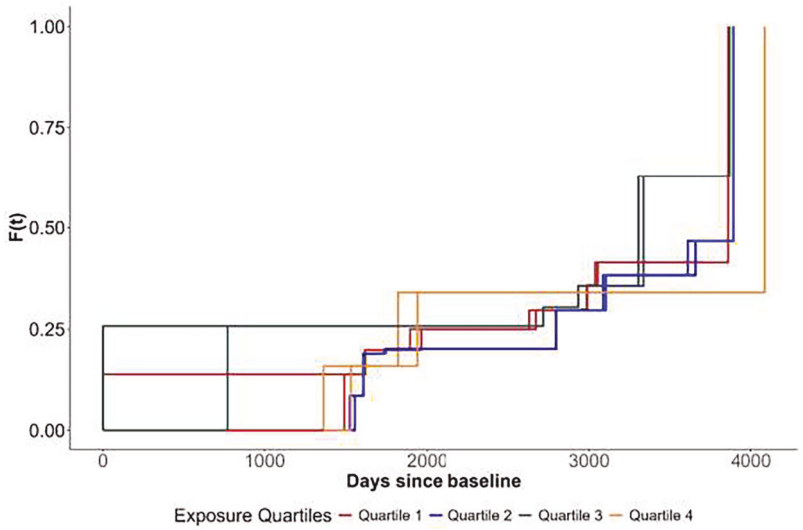
| Characteristic | Overall, N = 452[a] | Quartile 1, N = 113[a] | Quartile 2, N = 113[a] | Quartile 3, N = 113[a] | Quartile 4, N = 113[a] |
|---|---|---|---|---|---|
| Age in years | 63.0 (56.0, 69.0) | 64.0 (57.0, 70.0) | 63.0 (59.0, 69.0) | 62.0 (56.0, 68.0) | 61.0 (53.0, 66.0) |
| Male sex | 125 (27.7%) | 15 (13.3%) | 23 (20.4%) | 38 (33.6%) | 49 (43.4%) |
| Education: Less than high school | 83 (18.5%) | 23 (20.5%) | 23 (20.5%) | 16 (14.3%) | 21 (18.6%) |
| Income: ≥$40,000/year | | | | | |
| Poor | 54 (13.7%) | 23 (24.2%) | 12 (12.0%) | 10 (10.1%) | 9 (9.0%) |
| Lower-middle | 115 (29.2%) | 30 (31.6%) | 28 (28.0%) | 30 (30.3%) | 27 (27.0%) |
| Upper-middle | 111 (28.2%) | 16 (16.8%) | 35 (35.0%) | 27 (27.3%) | 33 (33.0%) |
| Affluent | 114 (28.9%) | 26 (27.4%) | 25 (25.0%) | 32 (32.3%) | 31 (31.0%) |
| Insured | 408 (90.5%) | 101 (89.4%) | 103 (91.2%) | 103 (92.0%) | 101 (89.4%) |
| Currently smoking | 41 (9.2%) | 7 (6.3%) | 14 (12.7%) | 10 (8.9%) | 10 (8.8%) |
| Alcohol consumption in the past year | 163 (36.1%) | 34 (30.1%) | 29 (25.7%) | 52 (46.0%) | 48 (42.5%) |
| Physical activity | | | | | |
| Poor Health | 222 (49.2%) | 59 (52.2%) | 47 (41.6%) | 60 (53.6%) | 56 (49.6%) |
| Intermediate Health | 128 (28.4%) | 34 (30.1%) | 33 (29.2%) | 27 (24.1%) | 34 (30.1%) |
| Ideal Health | 101 (22.4%) | 20 (17.7%) | 33 (29.2%) | 25 (22.3%) | 23 (20.4%) |
| Coronary heart disease history | 34 (7.5%) | 9 (8.0%) | 6 (5.3%) | 9 (8.0%) | 10 (8.8%) |
| History of stroke | 25 (5.5%) | 13 (11.5%) | 4 (3.5%) | 5 (4.4%) | 3 (2.7%) |
| History of myocardial infarction | 23 (5.1%) | 5 (4.4%) | 5 (4.4%) | 6 (5.3%) | 7 (6.2%) |
| Chronic kidney disease | 21 (4.7%) | 6 (5.3%) | 11 (9.8%) | 3 (2.7%) | 1 (0.9%) |
| BMI, kg/m^2 | 31.3 (27.8, 36.5) | 29.1 (26.3, 34.1) | 30.5 (27.0, 35.2) | 32.5 (29.0, 37.3) | 33.0 (29.1, 37.7) |
| SBP, mmHg | 128 (118, 137) | 128 (120, 138) | 128 (118, 138) | 128 (117, 137) | 127 (117, 133) |
| DBP, mmHg | 73.9 ± 8.0 | 73.0 ± 8.4 | 74.1 ± 7.3 | 73.7 ± 7.6 | 74.9 ± 8.6 |
| Diabetes | 160 (35.9%) | 33 (29.7%) | 36 (32.7%) | 46 (41.1%) | 45 (39.8%) |
| Total cholesterol, mg/dL | 200 (178, 223) | 201 (181, 224) | 204 (170, 226) | 203 (181, 219) | 195 (179, 216) |
| LDL cholesterol, mg/dL | 124 ± 35 | 126 ± 35 | 123 ± 38 | 126 ± 33 | 123 ± 34 |
| HDL cholesterol, mg/dL | 52.0 (43.0, 61.0) | 55.0 (45.0, 63.0) | 52.0 (44.3, 62.0) | 53.0 (42.3, 62.0) | 48.0 (41.0, 55.0) |
| eGFR, ml/min/1.73 m^2 | 90.2 (76.1, 103.9) | 92.4 (79.7, 104.1) | 84.3 (74.6, 99.1) | 89.1 (76.1, 104.4) | 93.0 (79.3, 107.9) |
| ACR | 6.1 (4.3, 12.2) | 6.4 (4.7, 11.3) | 6.9 (4.1, 13.9) | 5.7 (3.9, 9.8) | 6.1 (4.8, 13.5) |
| CRP, mg/L | 0.3 (0.1, 0.6) | 0.4 (0.2, 0.8) | 0.3 (0.2, 0.5) | 0.3 (0.1, 0.7) | 0.3 (0.1, 0.5) |
| 24-hour urine sodium excretion, mg | 3669 (2547, 4698) | 1840 (1449, 2208) | 3105 (2829, 3358) | 4117 (3887, 4370) | 5635 (5152, 6279) |
| Statin use | 105 (23.2%) | 21 (18.6%) | 30 (26.5%) | 30 (26.5%) | 24 (21.2%) |
| ACEI use[b] | 155 (34.3%) | 25 (22.1%) | 34 (30.1%) | 52 (46.0%) | 44 (38.9%) |
| ARB use[c] | 60 (13.3%) | 19 (16.8%) | 13 (11.5%) | 14 (12.4%) | 14 (12.4%) |
| Beta-Blockers use | 79 (17.5%) | 20 (17.7%) | 30 (26.5%) | 14 (12.4%) | 15 (13.3%) |
| Calcium Channel Blockers use | 128 (28.3%) | 32 (28.3%) | 31 (27.4%) | 34 (30.1%) | 31 (27.4%) |
| Diuretics use[d] | 281 (62.2%) | 69 (61.1%) | 69 (61.1%) | 70 (61.9%) | 73 (64.6%) |
| Other Antihypertensive Medication Classes[e] | 44 (9.7%) | 6 (5.3%) | 12 (10.6%) | 12 (10.6%) | 14 (12.4%) |
| Medication Adherence | | | | | |
| Incomplete record of medication use | 21 (4.6%) | 3 (2.7%) | 1 (0.9%) | 8 (7.1%) | 9 (8.0%) |
| No medication use | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Used all medications | 431 (95.4%) | 110 (97.3%) | 112 (99.1%) | 105 (92.9%) | 104 (92.0%) |

[a]Median (Q1, Q3); n (%); Mean ± SD.
[b]ACEI refers to Angiotensin-converting enzyme inhibitors.
[c]ARB refers to Angiotensin receptor blockers.
[d]Diuretics include Loop diuretics, Potassium-Sparing diuretic, and Thiazide diuretic.
[e]Other antihypertensive medication classes include Aldosterone Antagonist, Alpha-Blocker, Central Acting Agent, and Vasodilator.

**Table 2.** Incident rates and hazard ratios of incident apparent treatment resistant hypertension for JHS participants with hypertension enrolled in 2000–2004, by quartiles of urinary sodium.

| Incident aTRH | Quartiles of urinary sodium | | | | P Value for Trend[a] |
|---|---|---|---|---|---|
| | Quartile 1 (253 to 2530 mg) N = 113 | Quartile 2 (2553 to 3657 mg) N = 113 | Quartile 3 (3680 to 4692 mg) N = 113 | Quartile 4 (4715 to 9775 mg) N = 113 | |
| Cases, n (%) | 29 (25.7%) | 28 (24.8%) | 33 (29.2%) | 33 (29.2%) | 0.166 |
| Event Summary, | | | | | |
| At Visit 2 (cases/ no. at risk) | 17/96 | 16/100 | 25/97 | 19/102 | |
| At Visit 3 (cases/ no. at risk) | 12/64 | 12/75 | 8/64 | 14/73 | |
| HR (95% CI) | | | | | |
| Model 1ǂ | 1.00 (reference) | 0.88 (0.52, 1.51) | 1.14 (0.67, 1.94) | 1.04 (0.61, 1.80) | |
| Model 2§ | 1.00 (reference) | 0.66 (0.32, 1.35) | 0.95 (0.50, 1.82) | 0.87 (0.44, 1.70) | |
| Model 3‖ | 1.00 (reference) | 0.71 (0.34, 1.46) | 1.02 (0.50,2.06) | 0.95 (0.46, 2.00) | |

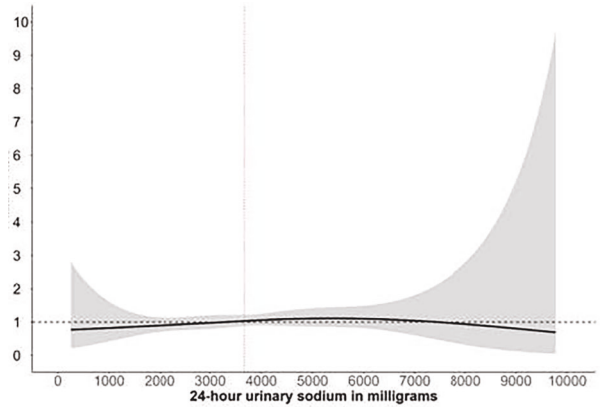
n (%) represents count (percentage).
Standard errors were estimated using.
ǂ Includes adjustment for age and sex.
§ Includes variables in model 1 and additional adjustment for smoking status, alcohol consumption, physical activity, BMI, diabetes, history of coronary heart disease, history of stroke, heart failure, chronic kidney disease, estimated glomerular filtration rate, low- and high-density lipoproteins, urinary albumin-to-creatinine ratio, medication adherence, and an indicator for each of six broad classes of antihypertensive medication used (ACEI, ARB, beta-blockers, calcium channel blockers, diuretics, and others).
‖ Includes variables in models 1 and 2 and additional adjustment for income, education, and insurance status.
*HR*, Hazard ratio; *CI*, confidence interval.
[a]The p-value for trend refers to the statistical test for trend across the quartiles of urinary sodium excretion.




| Exposure Quartiles | Days since baseline | | | | |
|---|---|---|---|---|---|
| | 0 | 1000 | 2000 | 3000 | 4000 |
| *Number of individuals at risk* | | | | | |
| **Quartile 1** | 113 | 77 | 56 | 14 | 0 |
| **Quartile 2** | 113 | 83 | 65 | 18 | 0 |
| **Quartile 3** | 113 | 72 | 57 | 17 | 0 |
| **Quartile 4** | 113 | 83 | 60 | 18 | 2 |

This figure shows cumulative incidence curves for aTRH across quartiles of 24-hour urinary sodium excretion. **Note:** The cumulative incidence curve shown above is the result from fitting a non-parametric maximum likelihood estimator (NPMLE) for univariate interval censored data guided by Turnbull's estimator. The parallel vertical lines represent the time intervals used in the Turnbull estimation process, which accounts for uncertainty in the exact timing of incident aTRH events. These intervals reflect the structure of follow-up assessments and are used to estimate cumulative incidence when exact event times are not observed.

**Fig. 2** Cumulative Incidence of aTRH by Quartiles of Urinary Sodium Excretion.




This figure presents adjusted hazard ratios for aTRH across quartiles of urinary sodium excretion, highlighting a non-linear association. **Note:** The hazard ratio for incident aTRH across restricted quadratic splines of urinary sodium (mg) with a single knot specified at the median value (red vertical line). The fitted model was a semi-parametric univariable hazards model suited for interval censored data.

**Fig. 3** Hazard Ratios for Incident aTRH by Urinary Sodium Excretion.

an association between higher sodium intake and favorable socioeconomic status and certain health behaviors [47], but also with adverse metabolic profiles [48, 49]. Conversely, higher sodium levels were less prevalent among participants with history of stroke, chronic kidney disease, or those using ACE inhibitors or beta-blockers. This pattern may reflect reverse causality, as individuals with these conditions are likely to have received clinical advice to reduce sodium intake, resulting in lower urinary sodium excretion [50]. The duality of association, where high sodium is linked to both favorable lifestyle behaviors and adverse health outcomes, has been shown in other studies [46].

The primary strength of this study is that it is a prospective, community-based observational study examining the association between urinary sodium and incident aTRH among AA adults in the United States. By using a biological measure of sodium, this study offers a more reliable assessment compared to self-reported dietary recall methods. However, some limitations should be acknowledged. First, the relatively small sample size and the limited number of aTRH cases led to wide confidence intervals, indicating some uncertainty in our estimates may have reduced the statistical power to detect statistically significant associations. Second, the observational nature of the study precludes causal inferences, as residual confounding by unmeasured variables cannot be ruled out [51]. Third, many participants had missing urinary sodium data, possibly due to challenges such as time-intensive nature of the procedure and participant burden. These challenges highlight the need for alternative approaches to collecting dietary sodium intake in large cohort studies like the JHS. Although 24-hour urine collection is considered the gold standard, its accuracy depends on participant compliance and completeness of collection. Incomplete collections may lead to systematic misclassification, as less compliant individuals will collect less urine and may appear to have lower sodium intake. Our study did not include validation procedures to assess completeness, which may introduce bias. In addition, sodium excretion was measured at a single 24-hour period, which may not accurately reflect long-term intake [52, 53], as repeated 24-hour urine collections were not used in this study. Patients with non-missing 24-hour urine samples were older, had a lower proportion of men, and showed differences in medication adherence when compared to those with missing samples at baseline, as quantified by the absolute standardized mean difference (Supplementary Table 2). This may have introduced selection bias, potentially affecting the generalizability of the findings. A further limitation is that sodium intake was assessed only at baseline, under the assumption that levels remained stable over time; however, urinary sodium can vary substantially even over short follow-up periods. Additionally, this study was conducted at a single site, reflecting the cultural and dietary patterns of a specific region and population, which limits the generalizability of our findings to other populations with different cultural, dietary, and socioeconomic factors. Finally, there were only 2 follow-up measurements, and this may not accurately reflect the true incidence of aTRH.

This study has important research and policy implications. Future research should employ longitudinal designs with repeated 24-h urine collection to better capture measures of long-term sodium intake on BP. Larger studies are also needed to provide more robust evidence of the association between sodium intake and aTRH, as the small sample size and limited number of aTRH cases in our analysis may have limited the statistical power to detect significant associations. Further, multiple factors associated with hypertension including genetic, lifestyle and dietary components, should be considered, with large randomized controlled trials to establish causality. Subgroup analyses could tailor public health recommendations to specific populations, and identifying biomarkers that associate sodium to BP will help in developing targeted interventions. Finally, evaluating the effectiveness of public health strategies aimed at reducing sodium intake and their associations with hypertension prevalence and outcomes will be essential for informing more effective prevention and treatment strategies.

## CONCLUSION

This community-based cohort study highlights the high sodium intake among AA adults with hypertension. Although our study did not find a significant association between 24-hour urinary sodium excretion and incident aTRH, the high levels of sodium intake observed in the AA population highlight the importance of continued public health efforts to reduce sodium consumption, given its well-established role in hypertension and related health risks. Larger, longitudinal studies are needed to confirm these findings and explore the complex associations between sodium intake, other dietary components, lifestyle factors, and genetics in hypertension management. Addressing these gaps could help reduce health disparities and improve health outcomes for AA adults.

## SUMMARY TABLE

What is known about this topic

- Hypertension is a leading cause of cardiovascular disease and disproportionately affects African American (AA) adults.
- Apparent treatment-resistant hypertension (aTRH) is highly prevalent among AA adults.
- Sodium intake is associated with blood pressure (BP) levels, but the relationship between sodium intake and the risk of developing aTRH in AA adults remains unclear.

What this study adds

- This study examined the association between 24-hour urinary sodium excretion and incident aTRH among AA adults with hypertension, using data from the Jackson Heart Study (JHS).
- The study found no statistically significant association between urinary sodium excretion and incident aTRH over a median follow-up of approximately 7.5 years.
- The findings suggest that the relationship between sodium intake and hypertension-related outcomes may be more complex than previously understood, indicating the need for further research considering factors such as genetics, other dietary components, and clinical conditions.

## DATA AVAILABILITY

The datasets generated during and/or analyzed during the current study are available from the Jackson Heart Study through the National Heart, Lung, and Blood Institute (NHLBI) Biologic Specimen and Data Repository Information Coordinating Center (BioLINCC) at https://biolincc.nhlbi.nih.gov/studies/jhs/.

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## AUTHOR CONTRIBUTIONS

All authors approved the final version of the manuscript. OAS, APB – Conceptualization, methodology, data curation, preparation of the first draft. DKA- Data management, data analysis and revision of manuscript. JDS, AJC, DS, ST, KLT, JAJ, and CGD – Critical review and revision of the manuscript.

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## ETHICAL APPROVAL

The Jackson Heart Study (JHS) received ethical approval from the Institutional Review Boards (IRBs) of Jackson State University, Tougaloo College, and the University of Mississippi Medical Center in Jackson, Mississippi. All methods were performed in accordance with relevant guidelines and regulations.

## COMPETING INTERESTS

The authors declare no competing interests.

## ADDITIONAL INFORMATION

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